ANTI-HER3 ANTIBODY AND USES THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to, and the benefit of, U.S. Provisional Application No. 62/688,628, filed Jun. 22, 2018, the contents of which are incorporated herein by reference in their entirety.

REFERENCE TO THE SEQUENCE LISTING

[0002] The present application is being filed along with a Sequence Listing in electronic format via EFS-Web. The Sequence Listing is provided as a text file entitled "Sequence listing", which is 11 kilobyte in size. The information in the electronic format of the Sequence Listing is incorporated herein by reference in its entirety.

BACKGROUND

Field of the Invention

[0003] The present invention relates to antibodies that specifically bind human human epidermal growth factor receptor 3 (also known as ERBB3 or HER3 antibody), methods for their production, pharmaceutical compositions containing said antibodies, and uses thereof.

Description of the Related Art

SUMMARY

[0004] The human epidermal growth factor receptor 3 (ErbB3, also known as HER3) is a receptor protein tyrosine kinase and belongs to the epidermal growth factor receptor (EGFR) subfamily of receptor protein tyrosine kinases, which also includes EGFR (HER1, ErbBI), HER2 (ErbB2, Neu), and HER4 (ErbB4) (Plowman et al, (1990) Proc. Natl. Acad. Sci. U.S.A. 87:4905-4909; Kraus et al, (1989) PNAS 86:9193-9197; and Kraus et al, (1993) PNAS 90:2900-2904). Like the prototypical EGFR, the transmembrane receptor HER3 consists of an extracellular ligand-binding domain (ECD), a dimerization domain within the ECD, a transmembrane domain, an intracellular protein tyrosine kinase-like domain and a C-terminal phosphorylation domain. The ectodomains of the ErbB receptors are further characterized as being divided into four domains (I-IV). Domains I and III of the ErbB ectodomain are involved in ligand binding (see, e.g., Hynes et. al. (2005) Nature Rev. Cancer 5, 341-354). Unlike the other HER family members, the kinase domain of HER3 displays very low intrinsic kinase activity.

[0005] The complex signaling network of the ErbB family members is tightly regulated in normal human tissue. However, dysregulation of ErbB family members by receptor overexpression, alteration of receptor functions by mutations or aberrant stimulation by ligands is often associated with the development and propagation of cancer. EGFR is frequently overexpressed in colorectal cancer, ovarian cancer, head and neck squamous cell carcinoma and other cancer types and EGFR overexpression has been linked to poor prognosis. HER2 is particularly associated with human breast cancer, where it is amplified and/or overexpressed in up to 30%.

[0006] HER3 has potent activation of the PI3K/Akt pathway which has been reported to be responsible for resistance mechanisms against ErbB targeted therapies (Holbro et al., 2003, PNAS 100:8933-8938). For example, the overexpression of HER3 receptor is a marker of acquired resistance of lung cancer to gefitinib and lapatinib.

[0007] The ligands neuregulin 1 (NRG) or neuregulin 2 bind to the extracellular domain of HER3 and activate receptor-mediated signaling pathway by promoting dimerization with other dimerization partners such as HER2. Heterodimerization results in activation and transphosphorylation of HER3's intracellular domain and is a means not only for signal diversification but also signal amplification. In addition, HER3 heterodimerization can also occur in the absence of activating ligands and this is commonly termed ligand-independent HER3 activation. For example, when HER2 is expressed at high levels as a result of gene amplification (e.g. breast, lung, ovarian or gastric cancer) spontaneous HER2/HER3 dimers can be formed. In this situation the HER2/HER3 is considered the most active ErbB signaling dimer and is therefore highly transforming.

[0008] It has previously been shown that also HER3 is mutated in ~11% of colon and gastric cancers which promotes oncogenic signaling in presence of HER2 (Jaiswal et al., 2013, Oncogenic ErbB3 mutations in human cancers. Cancer Cell 23, 603-617). These gain-of-function mutations in the HER3 pseudokinase domain enhance the allosteric activator potential of HER3.

[0009] Heterodimerization of HER3 with EGFR or HER2 also plays a role in oncogenic signaling by the HER family and contributes to cellular mechanisms that cause resistance to cancer therapeutics targeting EGFR and HER2. Heterodimerization results in activation of the ErbB receptor kinase domain and cross-phosphorylation of the ErbB receptors, which is known to occur between, e.g., EGFR and HER2, HER2 and ErbB3, and HER2 and ErbB4, and EGFR and ErbB3. The design of next-generation inhibitors that could overcome this developed resistance is now focused on directly targeting HER3 or HER3-containing heterodimers

[0010] Markedly elevated levels of HER3 have been found in several types of cancer such as breast, lung, gastrointestinal and pancreatic cancers indicating that ErbB3, like EGFR and HER2, plays a role in human malignancies. Interestingly, a correlation between the expression of HER2/HER3 and the progression from a non-invasive to an invasive stage has been shown (Alimandi et al, (1995) Oncogene 10:1813-1821; DeFazio et ai, (2000) Cancer 87:487-498; Naidu et al, (1988) Br. J. Cancer 78: 1385-1390). Accordingly, agents that interfere with HER3 mediated signaling are needed.

[0011] ErbB family members can be targeted with antibodies. They can inhibit ligand binding and/or receptor dimerization. Furthermore, antibodies can induce receptor internalization and degradation by receptor crosslinking (Friedman et al, 2005, PNAS 102: 1915-1920; Roepstorff et al, 2008, Histochem Cell Biol. 129:563-578; Moody et al., 2015, Mol. Therapy 23: 1888-1898). Additionally, antibodies containing an Fc part can mediate cancer cell killing through effector functions like antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC). Antibodies can also be used as delivery system for cytotoxic agents to cancer cells. Because of its emerging role as heterodimerization partner involved in propagating tumorigenesis and the development of resistance to therapy,